NDA 16-012/S-050; S-051; S-052

Merck Research Laboratories
Attention: Dennis M. Erb, Ph.D.
Sumneytown Pike, P.O. Box 4
BLA-20
West Point, PA 19486

APR 11 2000

Dear Dr. Erb:

Please refer to your supplemental new drug applications dated August 27, 1998, April 14, 1999, and March 3, 2000, received September 1,1998, April 19, 1999, and March 6, 2000, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VIVACTIL (protryptyline HCI), 5 mg and 10 mg Tablets.

Supplemental application S-050 provides revised final printed labeling (7904024) that incorporates the following changes:

1. Under the Drug Interactions Subsection of PRECAUTIONS, a statement was included about a drug interaction between tricyclic antidepressants and tramadol hydrochloride, based on published literature. This statement reads:

   "Tricyclic antidepressants may enhance the seizure risk in patients taking ULTRAM (tramadol hydrochloride)."

2. Under PRECAUTIONS, a new Geriatric Use subsection was added in conformance with the FDA Final Rule (201.57(f)(10)(ii)(A). This text was taken verbatim from this regulation and it reads:

   "Geriatric Use
   Clinical studies of VIVACTIL did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

3. Under the HOW SUPPLIED section, the Unit of Use package size was deleted.

Supplemental application S-051 provides revised final printed labeling (7904025) that incorporates the following changes;

1. Under the CONTRAINDICATIONS section, a statement was added about the contraindication of VIVACTIL in patients taking cisapride, based on a Dear Health Professional letter dated June 26, 1998, and it reads:

   "VIVACTIL is contraindicated in patients taking cisapride because of the possibility of adverse cardiac interactions including prolongation of the QT interval, cardiac arrhythmias and conduction system disturbances."

2. Under the HOW SUPPLIED section, the description of the tablet image was revised to reflect the complete image, i.e., the trademark "VIVACTIL on the other [side]."

Supplemental application S-051 provides revised final printed labeling (7904026) that incorporates the following changes:

1. Under the DESCRIPTIONS and HOW SUPPLIED section, the description and references to the 5 mg tablet was deleted to reflect the discontinuation of the 5 mg tablet.

2. Under the HOW SUPPLIED section, the National Stock Number for the 10 mg tablet was deleted and the storage statement was revised to reflect current stability data. The new storage statement reads:

   "Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature], Keep container tightly closed."

We note that these "Change Being Effected" supplemental applications have already been implemented.

We have completed the review of these supplemental applications (S-050, S-051, and S-052) and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the final printed labeling (copy code 7904026) submitted on March 3, 2000. Accordingly, these supplemental applications are approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH,HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Mr. Paul David, Regulatory Management Officer, at (301) 594-5530.

Sincerely,

Russell Katz, M.D.
Division Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research